UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/598,916	07/09/2007	Naoya Kojima	P30703	2020

7055 7590 05/18/2009

GREENBLUM & BERNSTEIN, P.L.C.
1950 ROLAND CLARKE PLACE
RESTON, VA 20191

EXAMINER	
POPA, ILEANA	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
05/18/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

gbpatent@gbpatent.com
pto@gbpatent.com

Office Action Summary	Application No.	Applicant(s)	
	10/598,916	KOJIMA ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9 and 10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/16/2009* .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-8 have been cancelled. Claim 9 has bee amended. Claim 10 is new. Claims 9 and 10 are pending and under examination.

2. All rejections pertaining to claims 1-3 and 8 are moot because Applicant cancelled the claims in the reply filed on 01/16/2009.

The rejection of claim 9 under 35 U.S.C. 103(a) as being unpatentable over Shimizu et al. (Bioorganic and Medicinal Chemistry, 2003, 11: 1191-1195), in view of each Wang et al. (Chin Med J, 2000, 113: 281-285), Hagiwara et al. (Cancer Research, 1993, 53: 687-692), Kole et al. (J. Infect. Dis., 1999, 180: 811-820), and Babincova et al. (Bioelectrochemistry, 2002, 55: 17-19) is withdrawn in response to Applicant's amendments to the claims filed on 01/16/2009. Specifically, Applicant amended the claim to recite a method for treating cancer, limitation not taught by the combination of the references cited above.

Information Disclosure Statement

3. The IDS form of 01/16/2009 has been considered. It is noted that the Mizuochi reference has been lined through because Applicant did not provide an English translation of the document, nor did Applicant provide an English abstract. Similarly, the English language abstract of the document GB 2 013 087 has been lined through because Applicant did not provide the document. Therefore, these documents were not

considered by the Examiner. Additionally, since English translations were not provided, the following documents were only considered with respect to their English language abstracts: JP 54-113414, Fujiwara et al., and Shimoma et al.

New rejections

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koenen et al. (Cancer Immunol Immunother, 1996, 42: 310-316, of record), in view of each Kawakami et al. (Gene Therapy, 2000, 7: 292-299), Kole et al. (J. Infect. Dis., 1999, 180: 811-820, of record), and Babincova et al. (Bioelectrochemsitry, 2002, 55: 17-19, of record).

Koenen et al. teach a method of treating cancer via intraperitoneal administration of cancer immunotherapeutic agents such as GM-CSF, wherein intraperitoneal administration activates peritoneal macrophages to exhibit killing activity against local tumors (Abstract; p. 310, column 2; p. 311, column 1; p. 314, column 2, second full paragraph; p. 315, column 1).

Koenen et al. do not teach oligosaccharide-coated liposomes (claim 9). However, doing such is suggested by the prior art. For example, Kawakami et al. teach

enhanced delivery to intraperitoneal macropahges by intraperitoneally administering therapeutic agents incorporated into mannosylated liposomes; enhanced delivery takes place by the internalization of mannosylated liposomes via receptor-mediated endocytosis (Abstract; p. 292, column 2; p. 297, column 1). Kole et al. teach that the intraperitoneal administration of therapeutic agents incorporated into mannosylated liposomes results in enhanced delivery to macrophages, as compared to non-mannosylated liposomes or therapeutic agent alone (Abstract). Based on these teachings, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Koenen et al. by delivering GM-CSF incorporated into the mannosylated liposomes as taught by Kawakami et al. and Kole et al., with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to enhance the delivery of GM-CSF to macrophages. One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches that mannosylated liposomes can be successfully used for enhanced delivery of therapeutic agents to macrophages. With respect to the limitations of delivery to the greater omentum or the extranodal lymphatic tissue in the mesentery (claim 9), the method of Koenen et al., Kawakami et al., and Kole et al. must necessarily result in such because all that is required for delivery to the greater omentum or mesentery is intraperitoneal administration.

Koenen et al., Kawakami et al., and Kole et al. do not teach administering their mannosylated liposomes in combination with oligosaccharide-coated liposomes encapsulating a magnetic compound (claim 10). Babincova et al. teach the use of

liposomes encapsulating a magnetic compound for the site-specific delivery of anti-cancer therapeutic, wherein the exposure of the liposomes to a magnetic field leads to local hyperthermia followed by the release of therapeutic agent from the liposomes (Abstract, p. 117, column 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Koenen et al. and Kawakami et al. by further concurrent administration of mannosylated liposomes encapsulating a magnetic compound, with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to obtain a composition capable of releasing the cancer immunotherapeutic agent from the macrophage at milky spots of omentum and mesentery, which are taught by the art to be important sites for tumor dissemination (see Koenen et al., p. 310, column 2, p. 315, column 1). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that liposomes encapsulating magnetic compounds can be successfully made.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant's arguments are answered below to the extent that they pertain to the instant rejection.

Applicant submits that one of skill in the art would not have necessarily expected the omentum or mesentery to be the target tissue of a liposome composition for drug delivery. In support thereof, Applicant refers to a report by Ikehara et al. (Cancer Res.,

2006, 66:8740- 8748) which describes a novel carbohydrate recognition-based drug delivery and controlled release system. Applicant argues that Ikehara et al. show the unexpected result that oligomannose-coated liposomes injected into the peritoneal cavity accumulate in the omentum, whereas bare liposomes are deposited in the liver (see page 8477 and Fig. 5B). Moreover, Applicant argues, although it is known that macrophages can accumulate in the milky spots of the omentum (see, e.g., Hagiwara et al. at page 687, second column, fifth paragraph), the distribution of liposome compositions susceptible to macrophage uptake does not appear to inherently result in accumulation of the liposome composition in the omentum. Furthermore, Applicant argues, Altin et al. (Methods 2006,40:39-52) disclose that normal liposomes administered to a patient can be taken up by immune cells, including antigen presenting cells (see, e.g. page 40, paragraph bridging first and second columns). However, as disclosed in Ikehara et al., the use of mannose-coated liposomes results in the delivery of an anti-cancer agent to the greater omentum or mesentery at a degree which is not achieved or expected by the use of a normal liposome. Applicant argues that one of skill in the art would not have predicted the extent of the anti-cancer effect achieved by the instant invention. In particular, the oligosaccharide coated liposome of the present invention is efficiently taken up by macrophages, and the macrophages accumulate specifically at a target site such as the greater omentum, resulting in a particularly effective anti-cancer treatment. For example, the specification describes the incorporation of mannose-coated liposomes into peritoneal macrophages within one hour of peritoneal cavity administration of the TRITC-labeled BSA-bearing liposomes

(Example 2, page 17). This result shows that the uptake of mannose-coated liposomes by macrophages is quit rapid and highly efficient. Example 4 and Figure 3 also indicate that mannose-coated liposomes encapsulating an anti-cancer agent accumulate at a target site (the greater omentum) after intraperitoneal administration. In particular, Figure 3 shows that 60% or more of the administered anti-cancer agent is accumulated at a target site. Thus, these data also show that when a mannose-coated liposome compositions are administered intraperitoneally, the encapsulated agent (here an anti-cancer agent) accumulates at a target site. The high degree of accumulation of the anti-cancer agent at the target site, as well as the high uptake rate and high uptake ratio of mannose-coated liposomes by macrophages, suggests that the anti-cancer agent is taken up by macrophages very efficiently: a desired characteristic for an anti-cancer agent delivery system. Furthermore, since cancer treatment with liposome compositions is a multi-step process comprising incorporation of the anticancer agent into an oligosaccharide coated liposome, then uptake of the liposome into a macrophage followed by the delivery of the macrophage to the target site, the high uptake ratio achieved by the instant invention improves the efficiency of drug delivery at an important early step prior to delivery of the anti-cancer agent to the target site. Applicant further submits that Example 3 of the instant specification describes the accumulation of macrophages at the target site, that Figure 2 shows the maximum accumulation of mannose-coated liposomes containing a fluorescence-labeled protein within 12 hours of administration, and that this accumulation is maintained for at hours. The results described in Example 3 and Figure 2 therefore show that liposome-containing

macrophages are delivered to and accumulate at the target site rapidly. In Example 4(2) on pages 19-20 of the specification, gastric cancer cells were transplanted in the peritoneal cavity of a mouse, and oligosaccharide-coated liposomes containing an anti-cancer agent and oligosaccharide-coated liposomes encapsulating magnetic fine particles were administered thereto. Magnetic field irradiation was then carried out hours after liposome administration. After one week, the effect of the anti-cancer agent was evaluated, and the results are shown in Figures 4-6. In particular, Figure 5 shows tumor reduction of 80% in mice treated with the anti-cancer drug as compared to control mice. As mentioned above, the oligosaccharide-coated liposome composition of the present invention containing an anti-cancer agent rapidly accumulated in the target site via macrophage uptake. The concentration of anti-cancer agents in the target site was high, and as a result a high therapeutic effect can be achieved. The qualitative and quantitative data shown in Figures 4 through 6 indicate that significant tumor reduction can be achieved. Such a high therapeutic effect would not be predicted by the any of the above-cited documents, either alone or in combination. Applicant submits that the unexpected results obtained by the present invention are sufficient to overcome any *prima facie* rejection of the claims.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

Applicant's arguments unexpected results are not found persuasive. First, Applicant was not the first to intraperitoneally administer mannosylated liposomes, the prior art teaches such (see the rejection above). Second, intraperitoneal administration

would necessarily result in (i) the omentum and mesentery to be the target tissue of a liposome composition for drug delivery, and (ii) the accumulation of the therapeutic agent to the target site. According to Applicant, the distribution of liposome compositions susceptible to macrophage uptake does not appear to inherently result in accumulation of the liposome composition in the omentum. Such is just an argument not supported by any evidence. All that is required to target liposomes to the omentum and mesentery or to accumulate the therapeutic agent to the target site is to intraperitoneally administer mannosylated liposomes. The instant claims and disclosure require nothing more than intraperitoneal administration to achieve accumulation at omentum, mesentery, and target site. The mere recognition of a latent property present in the prior art (in the instant case, accumulation at omentum, mesentery, and target site) does not equal unexpected results (see MPEP 2145 II). Moreover, it is noted that the prior art teaches that intraperitoneal administration of therapeutic agents results in increased macrophage accumulation into the milky spots in the omentum (see Koenen et al., Abstract, p. 315, column 1); therefore, Applicant was not the first to describe such. In conclusion, accumulation at omentum, mesentery, and target site are inherent to the method of Koenen et al., Kawakami et al., and Kole et al.

With respect to the argument that the use of mannose-coated liposomes results in the delivery at a degree which is not achieved or expected by the use of a normal liposome, it is noted that such was known in the prior art (see Kole et al., Abstract).

For all the reasons set forth above, Applicant's arguments are not found persuasive and the rejection is maintained.

Conclusion

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/

Primary Examiner, Art Unit 1633